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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/881,721	06/18/2001	Yair Reisner	01/21720	7956

7590 12/29/2003

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EXAMINER	
BELYAVSKYI, MICHAIL A	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/881,721	REISNER, YAIR	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,9-17 and 19-47* is/are pending in the application.

4a) Of the above claim(s) *22-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,9-17,19-21,46 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/23/03 has been entered.

Claims 1-5, 7, 9-17, 19-47 are pending.

Claims 22-45 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Claims 1-5, 7, 9-17,19-21 and 46-47, drawn to a method of inducing tolerance to transplant and method of transplanting a transplant, comprising a step of conditioning the recipient under sublethal, lethal or supralethal condition and wherein the transplant is a cell are under consideration in the instant application.

In view of the amendment, filed 10/23/03 the following rejection remains:

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-5, 7, 9-17, 19-21 and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,806,529 in view of Bachar-Lustig E et al. (Blood, 1999, v 94, pp 3212-3221) , or Mobest D et al.(Biotechnology and Bioengineering, 1998, v. 60 pp. 341-347), or Vavrova et al. (Hematol.Cell Ther. 1999, v.41 pp105-112) for the same reasons set forth in the previous Office Action, mailed 05/06/03.

Applicant's arguments, filed 10/23/03 have been fully considered, but have not been found convincing.

Applicant asserts that: (i) despite the fact that CD33+ cells had been known in the art at least 14 years, the tolerance-inducing activity of CD33+ cell had not been uncovered demonstrating that

there was no motivation to make the present invention; (ii) Vavrova et al. teaches culturing of autologous CD34+ cells for a autologous transplantation and growth conditions suitable for inducing veto activity that applies to a non-syngeneic donor-recipient pair, is not relevant.

Applicant is respectfully reminded that the rejection under 35 USC103 does not set any specific time frame when the attempts to combine the references should be made.

Applicants have traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Applicant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968). The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

Moreover, the Examiner failed to understand why growth conditions taught by Vavrova et al., are not relevant. Accoding to Stedman's Medical Dictionary, newly cited , autologous transplantation referring to transplantation in which the donor and recipient are the same individual. It is the Examiner's position that the growth conditions taught by Vavrova et al., are relevant for the current rejection under 35 USC103. In addition, it is noted that there is no recitation of syngeneic donor-recipient pair in the instant claims.

It is noted that the amended claims now recited culturing HPC population derived from a donor.

However, the '529 Patent teaches a method of inducing tolerance to a transplant during bone marrow transplantation comprising administering HPC cells derived from allogenic donor (see entire document, Abstract in particular) . The '529 Patent also teaches that host patient is conditioned prior to the transplantation of hematopoietic stem cells (HPC) . Conditioning may be carried out under sublethal, lethal or supralethal conditions (see column 3, lines 51-60 in particular). The '529 Patent also teaches that donor and recipient are both humans (see Example 1 in particular). The '529 Patent also teaches that said method enable engraftment of MHC-mismatched transplants (see column 2, lines 36-42 in particular).

The '529 Patent does not teaches that said HPC cells, derived from the donor are *ex vivo* culturing under growth conditions suitable for inducing or enhancing veto activity in at least a portion of said HPC cells and inducing differentiation of said HPC cells into $CD33^+$ myeloid phenotype cells prior to transplantation of the transplant.

Bachar-Lustig E. et al. teach that it is possible to culture HPC cells under growth conditions, suitable for inducing or enhancing tolerance-inducing activity of CD34+ cells by expanding *in vitro* the CD34+ cells and use them for transplantation (see entire document, abstract and page 3220 in particular). The said conditions are the same as to growth conditions disclosed in the instant specification (see Materials and Method in particular). It would be obvious to a person of ordinary skill in the art at the time the invention was made that the CD34+ HPC obtained and grown under the same conditions as disclosed in the instant specification would also be induced to differentiate into myeloid CD33+ cells with the same functional property as HPC recited in the instant claims absent a showing of unobvious property.

Mobest et al., teach *ex vivo* expansion of human CD34+ hematopoietic progenitor cells under condition suitable for inducing differentiation of said cells into $CD33^+$ myeloid phenotype cells (see entire document, Abstract in particular). Mobest et al., also teach that successful ex vivo culture and amplification of human CD34+ hematopoietic progenitor cells that would differntiate into $CD33^+$ myeloid phenotype cells offers the possibility of additional graft manipulation steps, e.g. depletion or elimination of contaminating tumor cells in Autologous grafts, amplification of bone marrow-repopulating hematopoietic cells, generation of immune effector cells, or genetic manipulation of stem cells (see page 341 in particular). The growth condition taught by Mobest et al. are the same as to growth conditions disclosed in the instant specification (see Materials and Method in particular). It would be obvious to a person of ordinary skill in the art at the time the invention was made that the CD34+ HPC obtained and grown under the same conditions as disclosed in the instant specification would also be induced to differentiate into myeloid CD33+ cells with the same functional property as HPC recited in the instant claims absent a showing of unobvious property.

Vavrova et al. teach a method of *ex vivo* expansion and differentiation of human HPC cells under growth conditions suitable for inducing or enhancing veto activity in at least a portion of said HPC cells and inducing differentiation of said HPC cells into $CD33^+$ myeloid phenotype cells (see entire document, Abstract and page 106 in particular). Vavrova et al. teach that *ex vivo* expansion of HPC would benefit studies including accelerated engraftment, reduced risk of infection, smaller stem cell harvest and improved effectiveness of genetically modified stem cells. The growth condition taught by Vavrova et al. are the same as to growth conditions disclosed in the instant specification (see Materials and Method and Table 3 in particular). It would be obvious to a person of ordinary skill in the art at the time the invention was made that the CD34+ HPC obtained and grown under the same conditions as disclosed in the instant specification would also be induced to differentiate into myeloid CD33+ cells with the same functional property as HPC recited in the instant claims absent a showing of unobvious property.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Bachar-Lustig E et al., or Mobest D et al., or Vavrova et al., to those of The '529 Patent, to obtain a claimed method of inducing tolerance to a transplant or a method of transplanting a transplant from a donor to a recipiet comprising a step of *ex vivo* culturing HPC, derived from the donor under growth conditions suitable for inducing or enhancing veto activity in at least a portion of said HPC cells and inducing differentiation of said HPC cells into $CD33^+$ myeloid phenotype cells prior to transplantation of the transplant.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because successful *ex vivo* culture and amplification of human CD34+ hematopoietic progenitor cells under growth conditions that would stimulated to differentiation of the said cells into $CD33^+$ myeloid phenotype cells prior to transplantation of the transplant offers additional possibility and would be beneficial in accelerated engraftment, reduced risk of infection, additional graft manipulation steps, e.g. depletion or elimination of contaminating tumor cells in autologous grafts, amplification of bone marrow-repopulating hematopoietic cells, generation of immune effector cells, or genetic manipulation of stem cells as taught by Bachar-Lustig E et al., or Mobest D et al., or Vavrova et al. These *ex vivo* cultured , amplified and differentiated CD34+ hematopoietic progenitor cells can be further used in a method of inducing tolerance to a transplant during bone marrow transplantation taught by the '529 Patent. Since the growth condition taught by Bachar-Lustig E et al., or Mobest D et al., or Vavrova et al., are the same as to growth conditions disclosed in the instant specification it would be obvious to a person of ordinary skill in the art at the time the invention was made that the CD34+ HPC obtained and grown under the same conditions as disclosed in the instant specification would also be induced to differentiate into myeloid CD33+ cells with the same functional property as HPC recited in the instant claims absent a showing of unobvious property.

Claims 46 and 47 are included because it would be conventional and within the skill of the art to identify the optimum culturing conditions suitable for inducing myeloid differentiation of cultured HPSc. In addition, Mobest et al. teach the methodology of analyzing the role of individual components of culturing medium for inducing myeloid differentiation of cultured HPSc (see page 344 in particular). Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

4. No claim is allowed.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is (703) 308-4232. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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December 18, 2003

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